IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

	CRAIG HARRISON MILLER	Art Unit:	**1624**
Serial No:	**09/864,905**	Examiner:	**HONG LIU**
Filed:	**MAY 24, 2001**	Attorney Docket:	**T103 1421.1 (42565.0037.5)**
For:	**PHARMACEUTICAL COMPOSITIONS AND METHODS FOR USE**		

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Craig Harrison Miller, hereby state as follows:

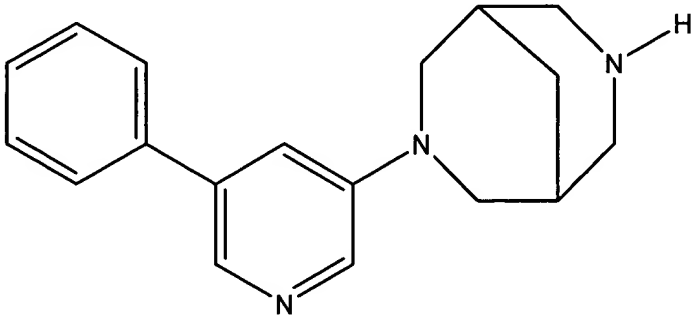
1. I am an applicant in the above-identified patent application and a co-inventor of the subject matter claimed in this application.

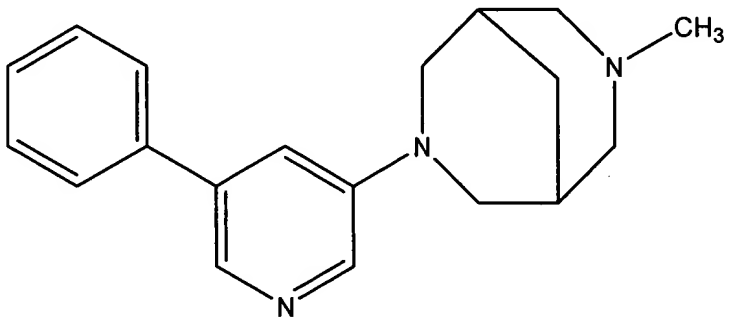
2. I have been a research scientist for more than twenty-five years, have performed research in all aspects of nicotinic receptor pharmacology, and am currently Scientific Director for Medicinal Chemistry at Targacept, Inc. My research has primarily focused on the synthesis of potential pharmaceutical agents and of specifically labeled compounds of interest as biological tracers. I am an author on nine issued patents (all in the area of nicotinic pharmacology) and twelve scientific papers. I received my B.S. degree in Chemistry in 1969 from Lewis and Clark College and my Ph.D. in Organic Chemistry in 1973 from the University of Illinois in Urbana-Champaign. Before joining Targacept, I taught chemistry at Salem College, where I hold the position of Professor Emeritus.

3. The invention claimed in the above-identified application relates, at least, to diazabicyclo[3.3.1]nonane compounds and pharmaceutical compositions including these compounds.

4. The principal prior art cited in this application is PCT WO 97/40049 to Czollner et al. ("Czollner"). Czollner teaches diazabicyclic compounds which require the presence of an aromatic or methyl group at position R22. The claimed compounds have two ring nitrogens, one of which is bound to a ring ("Cy"), and the other of which is bound to a hydrogen atom, and is in a position corresponding to position R22 on the Czollner compounds.

5. Compounds with a hydrogen and a methyl group attached at the R22 position (as this position is defined in Czollner) were prepared in order to compare, side by side, the binding of these compounds (i.e., the prior art compounds and the claimed compounds) to the nicotinic α4β2 receptor. The structure of these compounds is provided below:





6. The synthesis of the above-referenced compounds proceeded generally as follows. 7-Benzyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester was prepared by adding a methanolic solution containing benzylamine, 1-carbethoxy-4-piperidone and acetic acid to a methanolic suspension of paraformaldehyde (4 equiv.), and the solution was heated at reflux during the addition and for an additional two hours. The reaction mixture was cooled, neutralized, and extracted with ether, and the ether layer was washed, dried, filtered and concentrated under reduced pressure to give the crude product as a yellow oil (14.3 g, 95% yield). GC/MS analysis indicated 87% purity, and the product was carried on without purification.

7-Benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester was prepared by heating the carbamate formed above in an excess of hydrazine hydrate and potassium hydroxide in diethylene glycol/xylene. The product was distilled as a xylene-water azeotrope, which was cooled and extracted with ether. The ether extracts were washed, dried, filtered, and concentrated under reduced pressure to yield the desired product as a viscous, reddish-brown oil (12 g, >100%).

3-Benzyl-3,7-diazabicyclo[3.3.1]nonane was prepared by adding 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester to a 10 M solution of aqueous HCl, and refluxing the dark mixture for 6 hrs. The mixture was cooled and poured, neutralized with potassium hydroxide until a pH of approximately 12 was achieved, and extracted with ether. The ether extracts were washed, dried, filtered, and concentrated under reduced pressure to give a dark brown, viscous residue, which was distilled (Kugelrohr, air bath temp. approximately 120 C, 1 mm Hg) to give the desired product as a light yellow oil (2.3g, 38%).

3-Benzyl-7-(5-phenylpyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane was prepared by reacting 3-benzyl-3,7-diazabicyclo[3.3.1]nonane with 3-bromo-5-phenylpyridine, sodium t-butoxide, BiNAP and $Pd_2(dba)_3$. The dark reaction mixture was heated under reflux for 6 hours, and kept at room temperature overnight. The reaction mixture was diluted with ethyl acetate and filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel, eluting with 5% methanol/dichloromethane containing 0.1% ammonium hydroxide, to yield the desired product as a yellow oil (220 mg, 18%).

3-(5-Phenylpyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane di-p-toluenesulfonate was prepared by refluxing a methanolic solution of 3-benzyl-7-(5-phenylpyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane with a palladium (10% on carbon) catalyst and ammonium formate (500 mg). The mixture was cooled, filtered through Celite, and washed with methanol. The filtrate was concentrated under reduced pressure, and the residue treated with a solution of 10% KOH and extracted with dichloromethane (2x20 ml). The extracts were dried, filtered and concentrated to give the product as a brown oil. This oil was triturated with ether and the supernatant removed and treated with a solution of p-toluenesulfonic acid (0.6 mmol, 114 mg) in 2 ml of ether. The white precipitate was allowed to settle and the supernatant removed. The residue was suspended in a small volume of ether and heated gently while a minimum amount of methanol was added to achieve solution. On cooling, the pale yellow powder was collected and dried to give the product as the di-p-toluenesulfonate salt (114 mg, 61%) MP: 223-224°C.

3-Methyl-7-(5-phenylpyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane fumarate was prepared by refluxing a methanolic solution of 3-(5-phenylpyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane with 37% aqueous formaldehyde and formic acid for 4 hours. The

reaction mixture was concentrated under reduced pressure, and the residue was basified with a dilute potassium hydroxide solution and extracted with dichloromethane (3x10 ml). The extracts were dried, filtered and concentrated under reduced pressure to give a pale yellow oil. This oil was dissolved in warm THF and added to a warm solution of fumaric acid in 2 ml of THF. A white salt precipitated immediately and was collected by decanting the supernatant. The residue was taken up in a minimum amount of hot isopropanol and treated with THF to give a cloudy solution, which upon cooling provided the product as a white powder (20 mg, 54%).

7. As discussed above, the N-methyl compound was isolated as the fumarate salt, whereas the N-H compound was isolated as the di-p-toluenesulfonate salt. The structure of the compound itself determines its ability to bind to the relevant receptor, and variation in the salt form would not be expected to have a significant effect on the binding properties of the compounds.

8. The binding properties were assayed using substantially the same methods described in the above-identified application. When the binding properties of these compounds were compared side-by-side, the N-methyl compound bound to the nicotinic $\alpha4\beta2$ receptor with a K_i of 7.44 nM, whereas the N-H compound bound to the nicotinic $\alpha4\beta2$ receptor with a K_i of 0.18 nM (40-fold greater affinity). Thus, we have demonstrated that there is a substantial advantage, in terms of binding affinity, to the N-H compounds, as claimed, over the N-methyl compounds in the prior art.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

May 28, 2004
Date:

Craig Harrison Miller
Craig Harrison Miller